Art 34 Amdt.

CLAIMS

1. A use of a first agent that attenuates Topoisomerase II (Topo II) activity and a second agent that inhibits Heat Shock Protein 90 (HSP90) activity in the manufacture of a medicament for contemporaneous or sequential administration in chemotherapy wherein the first agent is selected from:

a Podophyllotoxin and derivatives and analogues thereof;
an Anthracenedione and derivatives and analogues thereof;
m-AMSA (amsacrine) and derivatives and analogues thereof;
a Bisdioxopiperazine and derivatives and analogues thereof.
a thiobarbiturate
Genistein and derivatives or analogues thereof; or
Pyrazoloacridine and derivatives or analogues thereof.

2. The use according to claim 1 wherein the first agent is a compound selected from:

(i) compounds that bind to Topo II and inhibit its activity (e.g. competitive inhibitors or allosteric inhibitors);
(ii) compounds which prevent the transcription, translation or expression of Topo II (e.g. ribozymes or antisense DNA molecules);
(iii) compounds which inhibit release of Topo II from intracellular stores; and
(iv) compounds which increase the rate of degradation of Topo II.

3. The use according to claim 1 or 2 wherein the first agent is a Podophyllotoxin and derivatives and analogues thereof and is selected from the group consisting of etoposide (VP16) or teniposide.

4. The use according to claim 1 or 2 wherein the first agent is the Anthracenedione Mitoxantrone.

5. The use according to claim 1 or 2 wherein the first agent a Bisdioxopiperazine and derivatives and analogues thereof and is selected from the group consisting of ICRF-154, 159, 187 or 193.

6. The use according to claim 1 or 2 wherein the first agent is the thiobarbiturate Merbarone or a derivative or analogue thereof.

7. The use according to any preceding claim wherein the second agent is a compound selected from:

(i) compounds that bind to Hsp90 and inhibit its activity (e.g. competitive inhibitors or allosteric inhibitors);

(ii) compounds which prevent the transcription, translation or expression of Hsp90 (e.g. ribozymes or antisense DNA molecules);

(iii) compounds which inhibit release of Hsp90 from intracellular stores; and

(iv) compounds which increase the rate of degradation of Hsp90.

8. The use according to claim 7 wherein the second agent is Geldanamycin or a derivative or analogue thereof.

9. The use according to claim 8 wherein the second agent is 17-Allylamino, 17-demethoxygeldanamycin (17AAG).

10. The use according to claim 7 wherein the second agent is Radicicol or a derivative or analogue thereof.

11. The use according to any preceding claim wherein the chemotherapy is for cancer treatment.

12. The use according to claim 11 for the treatment of solid tumours.

13. The use according to claim 12 for the treatment of bowel cancer, small cell and non-small cell lung cancer, head and neck cancer, breast cancer, bladder cancer or malignant melanoma.

14. The use according to claim 11 for the treatment of paediatric tumours.

15. The use according to claim 14 for the treatment of neuroblastoma, leukaemias and lymphomas.

16. The use according to claim 11 wherein the first agent is etoposide and it is used in the treatment of cancers selected from:

Adult Acute Myeloid Leukemia
Adult Hodgkin's Disease
Adult Non-Hodgkin's Lymphoma
AIDS-Related Lymphoma
Carcinoma of Unknown Primary
Childhood Acute Myeloid Leukemia
Childhood Brain Tumor
Childhood Cerebral Astrocytoma
Childhood Ependymoma
Childhood Hodgkin's Disease
Childhood Liver Cancer
Childhood Medulloblastoma
Childhood Non-Hodgkin's Lymphoma
Childhood Rhabdomyosarcoma
Childhood Supratentorial Primitive Neuroectodermal and Pineal Tumors
Childhood Visual Pathway and Hypothalamic Glioma
Endometrial Cancer
Ewing's Family of Tumors Including Primitive Neuroectodermal Tumor (PNET)
Extragonadal Germ Cell Tumors
Gastric Cancer
Gastrointestinal Carcinoid Tumor

Gestational Trophoblastic Tumor
Kaposi's Sarcoma
Malignant Thymoma
Neuroblastoma
Non-small Cell Lung Cancer
Osteosarcoma/Malignant Fibrous Histiocytoma of Bone
Ovarian Epithelial Cancer
Ovarian Germ Cell Tumor
Pediatric Extracranial Germ Cell Tumor
Prostate Cancer
Retinoblastoma
Small Cell Lung Cancer
Testicular Cancer
Unusual Cancers of Childhood
Wilms' Tumor and Other Childhood Kidney Tumors

17. The use according to any one of claims 1 - 10 wherein the chemotherapy is for:

antibacterial treatments;
antifungal treatments;
the treatment of AIDS/HIV;
the treatment of multiple sclerosis; or
the killing and inhibition of proliferation of any organism.

18. The use according to any preceding claim wherein the chemotherapy is for prophylactic treatment.

19. A delivery system for use in a gene therapy technique, said delivery system comprising:

(i) a first DNA molecule encoding for a protein which directly or indirectly attenuates Topoisomerase II activity; and

(ii) a second DNA molecule encoding for a protein which directly or indirectly inhibits Heat Shock Protein 90 activity;

wherein said DNA molecules are capable of being transcribed to allow the expression of said proteins and thereby be effective for chemotherapy.

20. The use of a delivery system according to claim 19 for the manufacture of a medicament for use in chemotherapy.

21. The use according to claim 20 for the treatment of conditions defined by any one of claims 11 to 18.

22. A method of screening a first and a second compound, to test whether or not said compounds has efficacy for use in combination as a chemotherapy, comprising:

(a) exposing said compounds to Topoisomerase II and evaluating whether or not said compounds bind thereto;

(b) exposing said compounds to Heatshock Protein 90 and evaluating whether or not said compounds bind thereto; and

(c) selecting a first and second compound, wherein at least one compound binds to Topoisomerase II and at least one compound binds to Heatshock Protein 90 for use in combination as a chemotherapy.

23. A method of screening compounds, to test whether or not said compounds have efficacy for use in chemotherapy, comprising:

(d) exposing said compounds to Topoisomerase II and evaluating whether or not said compounds bind thereto;

(e) exposing said compounds to Heatshock Protein 90 and evaluating whether or not said compounds bind thereto; and

selecting compounds that bind to Topoisomerase II and to Heatshock Protein 90 for use in chemotherapy.

24. The method according to claim 22 or 23 wherein the compound is screened using Topoisomerase II and Heatshock Protein 90 as binding partners in an interaction trap and evaluating whether or not said compound modulates binding.

25. The method according to claim 24 wherein the interaction trap is a yeast two-hybrid interaction trap.

26. The method according to claim 25 wherein yeast used in the interact trap are permeable to the tested compounds.

27. A method of screening a compound, to test whether or not said compound is carcinogenic, comprising exposing said compound to Topoisomerase II and Heatshock Protein 90 to evaluate whether or not said compound promotes interaction between Topoisomerase II and Heatshock Protein 90.

28. An *in vitro* method for diagnosing whether or not a subject has, or is likely to develop cancer, comprising:

(i) detecting the level of activity or expression levels of HSP90 and Topoisomerase II from a sample of cells from said subject; and

(ii) comparing the level of activity or expression levels of HSP90 and Topoisomerase II in said sample relative to activity expression levels of HSP90 and Topoisomerase II from a non-cancerous sample.

29. An *in vitro* method for evaluating the suitability of chemotherapeutic treatment for administration to a subject, comprising:

(i) detecting the level of activity or expression levels of HSP90 and Topoisomerase II from a sample of cells from said subject; and

(ii) comparing the level of activity or expression levels of HSP90 and Topoisomerase II in said sample relative to activity expression levels of HSP90 and Topoisomerase II from a non-cancerous sample.

30. An *in vitro* method for monitoring the effectiveness of a chemotherapy for treating a subject, comprising:

(i) detecting the level of activity or expression levels of HSP90 and Topoisomerase II from a sample of cells from said subject; and

(ii) comparing the level of activity or expression levels of HSP90 and Topoisomerase II in said sample relative to activity expression levels of HSP90 and Topoisomerase II from a non-cancerous sample.